

## Use of the terms "overdiagnosis" and "misdiagnosis" in the COPD literature: A rapid review

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## Key points

- In the COPD literature, the terms “overdiagnosis” and “misdiagnosis” are often used interchangeably and almost always refer to a false positive diagnosis.
- Use of spirometry with correct interpretation of the results can avoid a substantial proportion of cases of misdiagnosis of COPD.

## Educational aims

- To explore the use of the terms “overdiagnosis” and “misdiagnosis” in the COPD literature.
- To identify the main sources of overdiagnosis and misdiagnosis in COPD.

## Review

# Use of the terms “overdiagnosis” and “misdiagnosis” in the COPD literature: a rapid review

Challenges in the diagnostic process of chronic obstructive pulmonary disease (COPD) can result in diagnostic misclassifications, including overdiagnosis. The term “overdiagnosis” in general has been associated with variable definitions. In connection with efforts to reduce low-value care, “overdiagnosis” has been defined as a true positive diagnosis of a condition that is not associated with any harm in the diagnosed person. It is, however, unclear how the term “overdiagnosis” is used in the COPD literature. We conducted a rapid review of the literature to explore how the terms “overdiagnosis” and “misdiagnosis” are used in the context of COPD. Electronic searches of Medline were conducted from inception to October 2018, to identify primary studies that reported on over- and/or misdiagnosis of COPD using these terms. 28 articles were included in this review. Overdiagnosis and misdiagnosis in COPD were found to be used to describe five main concepts: 1) physician COPD diagnosis despite normal spirometry (14 studies); 2) discordant results for COPD diagnosis based on different spirometry-based definitions for airflow obstruction (10 studies); 3) COPD diagnosis based on pre-bronchodilator spirometry results (three studies); 4) comorbidities (e.g. heart failure or asthma) that affect spirometry and have clinical features which overlap with COPD (two studies); and 5) normalisation of abnormal (post-bronchodilator) spirometry at follow-up (one study). The terms “overdiagnosis” and “misdiagnosis” were often used interchangeably and almost always referred to a false positive diagnosis. Performing (technically correct) spirometry with correct interpretation of the results could probably reduce misdiagnosis in a large proportion of the misdiagnosed cases of COPD. In addition, guidelines need to provide a more acceptable consensus spirometric definition of airflow obstruction.

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## Background

Chronic obstructive pulmonary disease (COPD) is defined as “a preventable and treatable disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious

particles or gases, primarily caused by cigarette smoking” [1]. Despite COPD being a very common condition, there is no consensus on the diagnostic criteria for COPD [2]. COPD can be complex to diagnose, as a number of factors are relied upon to confirm the diagnosis, including a history of exposure to cigarette smoke or other noxious inhaled agents and the presence of chronic symptoms such

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**Overdiagnosis in the COPD literature generally refers to a false positive diagnosis (misdiagnosis). Misdiagnosis can be significantly reduced by performing spirometry in every patient with suspected COPD.** <http://ow.ly/zuAw30o7hiV>



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as cough, wheeze or dyspnoea, as well as confirmed persistent airflow limitation on spirometry.

Lack of consensus regarding diagnostic criteria relates in particular to spirometry-based definitions. A study that assessed the impact of four different widely used spirometry-based definitions of airflow obstruction and one self-reported definition demonstrated that the population prevalence estimate of COPD altered by as much as 200% depending on which definition was used [2]. The four spirometry-based definitions included: 1) forced expiratory volume in 1 s (FEV<sub>1</sub>)/forced vital capacity (FVC) <0.7 and FEV<sub>1</sub> <80% predicted (Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 2) [3]; 2) FEV<sub>1</sub>/FVC below the lower limit of normal (LLN) [4]; 3) FEV<sub>1</sub>/FVC <88% predicted in males and <89% predicted in females [5]; 4) FEV<sub>1</sub>/FVC <0.7 (“fixed ratio”) (GOLD stage 1) [3].

In clinical practice, the GOLD definition of airflow obstruction based on post-bronchodilator FEV<sub>1</sub>/FVC of <0.7 is probably the most commonly used because it can be easily calculated, although the American Thoracic Society and the European Respiratory Society recommend the use of age- and sex-specific LLN for FEV<sub>1</sub>/FVC [6].

The need to use spirometry to diagnose COPD poses additional challenges beyond the lack of consensus about what constitutes relevant airflow obstruction. Spirometry requires that health professionals are trained in spirometry technique and patients need to be able to perform reproducible breathing manoeuvres. In many settings, especially in resource-constrained areas, a spirometer might not be readily available.

These challenges (lack of consensus on the definition of airflow obstruction, poorly performed

spirometry and underuse of spirometry) can all have an impact on whether COPD is diagnosed in a patient or not and are associated with overdiagnosis, underdiagnosis and misdiagnosis of COPD.

The issues of overdiagnosis, underdiagnosis and misdiagnosis of COPD are not new. In recent years, there has been interest in overdiagnosis of different conditions, driven by an effort to address “too much medicine”, that is, healthcare interventions that have no net benefit for patients and may even result in harm [7]. In this context, overdiagnosis, especially related to cancer screening, has been defined as a true positive diagnosis of a condition that is not associated with any morbidity or mortality over a patient’s lifetime (for example, diagnosis of an *in situ* breast cancer in an elderly woman, which will not cause any symptoms during her lifetime and will not be the cause of her death [7]). Even though the prevalence of overdiagnosis and misdiagnosis of COPD has been reported widely in the literature, it is unclear how the terms “overdiagnosis” and “misdiagnosis” in the context of COPD have been used.

A previous review has focused on estimating the prevalence of COPD and identifying causes of underdiagnosis and overdiagnosis in different health systems but did not focus on the terminology used [8]. Additionally, there has been a scoping review on misdiagnosis in COPD [9]. We performed a review of the literature to assess how the term “overdiagnosis” is used in the context of COPD.

## Literature review

We conducted electronic searches of Medline from inception to October 2018 using the following search terms: “overdiagnosis” AND (COPD OR chronic obstructive pulmonary disease OR emphysema). We included original studies of any study design that reported on over- and/or misdiagnosis of COPD using these terms. We restricted our search to studies published in English. Relevant titles and abstracts were identified and eligible articles were included in this review. We also checked the reference lists of included studies.

From searches of Medline and PubMed, 42 records were identified, and a further 19 records were identified from reference list searches. From these we retrieved 50 articles for full-text review but 22 of these did not meet our selection criteria. 28 studies were included in our review (figure 1). The studies were published between 2003 and 2018 and were conducted in 13 countries.

## Definitions of overdiagnosis

In examining the 28 eligible studies, we identified several different types of “overdiagnosis” and “misdiagnosis”, which we have grouped in the categories described in the next sections and listed

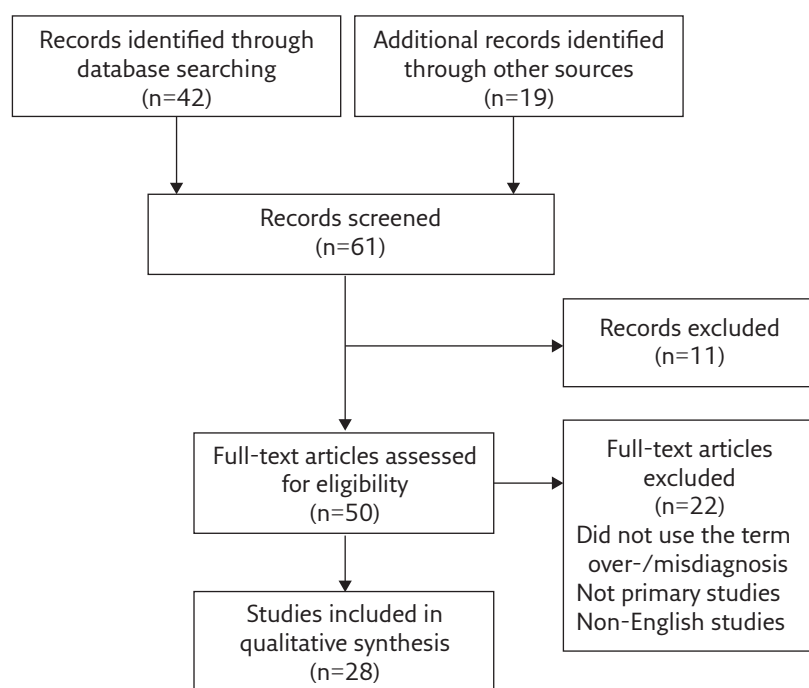


Figure 1 Study flow diagram.



in table 1. Further details on each of the included studies can be found in table 2.

## Physician COPD diagnosis, but with normal spirometry

15 studies reported overdiagnosis or misdiagnosis if the physician's diagnosis was discordant with the spirometry result, which showed either a normal or restrictive pattern [10–24]. A physician diagnosis with normal spirometry could have been a case in which the physician did not use spirometry to establish a diagnosis of COPD (and a normal spirometry was later found in the study) [10, 14–17, 21–23], or a case in which the physician "ignored" a normal spirometry result [12, 20, 24]. Most of these studies cited under-utilisation of spirometry as the primary cause of overdiagnosis and misdiagnosis in this context. Five studies used the term "overdiagnosis" to capture these discordant cases of physician diagnosis and spirometry readings [10–13, 17]. Eight studies considered these cases to be misdiagnosed [14, 15, 18–22, 24]. In two studies the terms "overdiagnosis" and misdiagnosis were used interchangeably to describe this concept [16, 23].

## Fixed threshold for the definition of (post-bronchodilator) airflow obstruction

10 studies examined the effect of the fixed FEV<sub>1</sub>/FVC ratio (GOLD criteria) threshold for diagnosis of airflow obstruction in COPD [10, 14, 15, 17, 25–30]. The FEV<sub>1</sub>/FVC ratio is known to decline with age, and a fixed diagnostic threshold of FEV<sub>1</sub>/FVC <0.7 after bronchodilator administration does not take this into account. These studies compared the effect on COPD prevalence when using the fixed ratio compared to an age-adjusted definition of airflow obstruction or the LLN. The majority of these studies used the term "overdiagnosis" to describe a situation in which airflow obstruction was present using a definition of an FEV<sub>1</sub>/FVC ratio <0.7, but not when using the LLN [10, 15, 17, 25–28]. VAN DIJK *et al.* [30] and STEINACHER *et al.* [29] used the terms "overdiagnosis" and "misdiagnosis" interchangeably when describing misclassification due to a diagnosis of airflow obstruction based on an FEV<sub>1</sub>/FVC ratio <0.7. Estimates of COPD overdiagnosis due to the fixed ratio ranged from 4.6% in a general population study that included people aged 40–80 years [27] to 42.7% in a study of people over the age of 80 years referred for spirometry by their general practitioners (GPs) [26].

## Use of pre-bronchodilator spirometry only

One study explored the impact of using pre-bronchodilator spirometry on COPD prevalence

**Table 1** Types of overdiagnosis and misdiagnosis

<b>1</b>	Physician COPD diagnosis despite normal spirometry The physician did not use spirometry to establish a diagnosis of COPD (and a normal spirometry was later found in the study) The physician "ignored" a normal spirometry result
<b>2</b>	Discordant results for COPD diagnosis based on different spirometry-based definitions for airflow obstruction ( <i>e.g.</i> post-bronchodilator FEV <sub>1</sub> /FVC <0.7 or FEV <sub>1</sub> /FVC <LLN)
<b>3</b>	COPD diagnosis based on pre-bronchodilator spirometry results
<b>4</b>	Comorbidities ( <i>e.g.</i> heart failure or asthma) that affect spirometry and have clinical features which overlap with COPD
<b>5</b>	Normalisation of abnormal (post-bronchodilator) spirometry at follow-up

[26]. To avoid misclassification with asthma (which is characterised by reversible airflow obstruction), a diagnosis of COPD must be based on airflow obstruction on spirometry performed after bronchodilator application. In the study of symptomatic adults referred for spirometry by their GPs, 25.3% of subjects with an obstructive pattern diagnosed by pre-bronchodilator spirometry were no longer classified as having COPD on post-bronchodilator spirometry. These cases were considered to be overdiagnosed.

Two studies reported misdiagnoses of physician-diagnosed COPD that later was found to be asthma after performing post-bronchodilator spirometry [19, 21].

## Alternative diagnosis overlapping with COPD

Two studies performed spirometry in patients with known heart failure and found that, in this population, a substantial proportion of those diagnosed with COPD (12.3% in the first study [17] and 19.1% in the second study [29]) had been misdiagnosed using a definition of airflow obstruction based on FEV<sub>1</sub>/FVC <0.7 rather than FEV<sub>1</sub>/FVC <LLN. There is considerable overlap between the clinical features of heart failure and COPD.

The authors of one study attempted to detect airflow obstruction that was possibly masked by heart failure-related restriction (in 13 cases with an FEV<sub>1</sub>/FVC >LLN and an FVC <LLN) by experimentally substituting measured FVC by 80% of predicted FVC. This led to a decline of FEV<sub>1</sub>/FVC to <0.7 in eight cases and <LLN in seven cases [29].

One study reported that 19.5% of patients newly diagnosed with asthma had previously received an incorrect diagnosis of COPD and/or emphysema [31]. These cases were considered to be misdiagnosed cases and were attributed to the overlap in clinical features of asthma and COPD.

**Table 2** Use of the terms "overdiagnosis" and "misdiagnosis" in the included studies

First author, year [ref.]	Population details	Terms used	Reason for classification as overdiagnosis	Estimated prevalence of overdiagnosis/misdiagnosis
<b>VAN DIJK, 2015 [30]</b>	Population study (n=4882) with sample aged $\geq 40$ years (mean $\pm$ SD age 57 $\pm$ 11 years), including former and current smokers; symptomatic; 4% had known chronic bronchitis	Overdiagnosis, misdiagnosis	Discordant results between 1) post-bronchodilator FEV <sub>1</sub> /FVC <0.7 but $\geq$ LLN; and 2) FEV <sub>1</sub> /FVC <0.7 + FEV <sub>1</sub> <80% predicted	Prevalence of spirometric airflow limitation was 17% by fixed ratio and 11% by LLN Patients who had airflow limitation meeting fixed ratio but not LLN were more likely to have cardiovascular disease (odds ratio 1.52)
<b>LLORDÉS, 2015 [10]</b>	Smokers aged $\geq 45$ years (n=1738), some with symptoms (21–46% depending on symptom); 10.5% pre-existing COPD diagnosis	Overdiagnosis	Normalisation of spirometry after 4 weeks of treatment COPD diagnosis despite no evidence of airflow obstruction on spirometry (defined as post-bronchodilator FEV <sub>1</sub> /FVC <0.7) Discordant results for COPD diagnosis based on post-bronchodilator FEV <sub>1</sub> /FVC <0.7 but $\geq$ LLN	In subjects with a new diagnosis of COPD by fixed ratio, 16% presented normal spirometry after 4 weeks of treatment 15.6% of people with physician-diagnosed COPD did not fulfil the spirometric criteria for COPD Prevalence of COPD using LLN was 15.5% compared to 24.3% using fixed ratio
<b>SPEIRO, 2017 [15]</b>	Patients admitted to a community teaching hospital (n=6018); aged $\geq 18$ years (mean $\pm$ SD age 69.5 $\pm$ 12.8 years); admitted for respiratory complaints with COPD as a principal or leading diagnosis and had spirometry performed during hospitalisation	Misdiagnosis, overdiagnosis	COPD diagnosis despite no evidence of airflow obstruction on spirometry, defined as post-bronchodilator FEV <sub>1</sub> /FVC <0.7 (no spirometry had been performed before the study) Discordant results for COPD diagnosis based on post-bronchodilator FEV <sub>1</sub> /FVC <0.7 but $\geq$ LLN	30.8% of cases of patients with a primary diagnosis of COPD had normal pulmonary function tests (COPD diagnosis is refuted) Significant correlation between presence of hypertension, obstructive sleep apnoea, coronary artery disease, congestive heart failure and misdiagnosis of COPD 10.7% of spirometry studies diagnosed as airflow obstruction by GOLD criteria would have been considered normal by LLN criteria (these patients were more likely never-smokers and asymptomatic)
<b>LAMPRECHT, 2011 [25]</b>	General population sample (n=1258), some with symptoms consistent with COPD; aged >40 years; 5.6% had a previous physician diagnosis of COPD, emphysema or chronic bronchitis	Overdiagnosis	Discordant results for COPD diagnosis based on post-bronchodilator FEV <sub>1</sub> /FVC <0.7 but $\geq$ LLN	6.4% of the study population had discordant obstructive cases (FEV <sub>1</sub> /FVC <0.7 and $\geq$ LLN) Discordant cases had similar profiles to those with restrictive disease and these subjects more often had diagnosis of heart disease than those with normal function

*Continued*

Table 2 Continued

First author, year [ref.]	Population details	Terms used	Reason for classification as overdiagnosis	Estimated prevalence of overdiagnosis/misdiagnosis
<b>SCHERMER, 2008 [26]</b>	Symptomatic adults (n=14056) referred for spirometry by their GP for suspected COPD; mean±sd age 53.0±21.4 years; 69% current/former smokers	Overdiagnosis	Discordant results for COPD diagnosis based on post-bronchodilator FEV <sub>1</sub> /FVC <0.7 but ≥LLN Only pre-bronchodilator spirometry result	Age years 31–40 8.9% 41–50 15.5% 51–60 23.9% 61–70 33.2% 71–80 38.7% ≥81 42.7% 25.3% of obstructive pattern diagnosed by pre-bronchodilator spirometry was not classified as COPD on post-bronchodilator spirometry 4.6% of subjects aged 40–80 years had overdiagnosed COPD
<b>GARCÍA-RIO, 2011 [27]</b>	General population sample (n=3802) aged 40–80 years, including smokers, some with symptoms consistent with COPD	Overdiagnosis	Discordant results for COPD diagnosis based on post-bronchodilator FEV <sub>1</sub> /FVC <0.7 but ≥LLN	
<b>WANG, 2013 [28]</b>	Population study (n=1382); sample aged 56–84 years (mean±sd age 67.7±13.3 years); never-smokers; asymptomatic; no previous diagnosis of asthma, COPD or heart disease	Overdiagnosis	Discordant results for COPD diagnosis based on post-bronchodilator FEV <sub>1</sub> /FVC <0.7 but ≥LLN	9.5% of asymptomatic population were diagnosed with COPD using the fixed criterion compared with 4.3% using the LLN (using spirometric reference values that were specifically derived for the study population in Jinan, China)
<b>FISHER, 2016 [14]</b>	Members of the 1921 birth cohort from North-East England recruited around their 85th birthday (n=845); >50% former smokers; symptomatic; 16.6% had previous diagnosis of COPD; median number of comorbid diseases was 5	Overdiagnosis, misdiagnosis	COPD diagnosis despite no evidence of airflow obstruction on spirometry, defined as either 1) post-bronchodilator FEV <sub>1</sub> /FVC <0.7, 2) FEV <sub>1</sub> /FVC <LLN, or 3) Global Lung Function Initiative criteria Discordant results for COPD diagnosis based on post-bronchodilator FEV <sub>1</sub> /FVC <0.7 but ≥LLN	75.6% of those with physician-diagnosed COPD met the GOLD criteria for spirometry; however, using the LLN only 41.1% had airflow obstruction 44.5% of the healthy reference group who were asymptomatic met the GOLD cut-off for COPD 24.4% of those with physician-diagnosed COPD did not satisfy spirometric criteria for COPD using GOLD criteria

Continued

Table 2 Continued

First author, year [ref.]	Population details	Terms used	Reason for classification as overdiagnosis	Estimated prevalence of overdiagnosis/misdiagnosis
<b>STEINACHER, 2012 [29]</b>	Consecutive patients of an outpatient heart failure clinic (n=89); median age 67.0 years; 55% former/current smokers; 12.4% with self-reported COPD; majority New York Heart Association class II heart failure	Overdiagnosis, misdiagnosis	COPD diagnosis despite no evidence of airflow obstruction on spirometry, defined as post-bronchodilator FEV <sub>1</sub> /FVC <0.7 Discordant results for COPD diagnosis based on post-bronchodilator FEV <sub>1</sub> /FVC <0.7 but ≥LLN Heart failure affects spirometry interpretation; clinical symptoms overlapping with those of COPD	Among participants who did not demonstrate airflow obstruction on spirometry, 6% had a previous diagnosis of COPD; these 6% were identified as false positives by the GOLD criteria Application of the GOLD criteria led to a significantly higher rate of COPD in the heart failure population (43.8%) compared to using the LLN (24.7%) 12.3% patients who presented an FEV <sub>1</sub> /FVC >0.7 had an FVC <LLN and had measured FVC experimentally substituted by 80% of predicted FVC, to detect airflow obstruction that was possibly masked by heart failure-related restriction; this led to a decline in FEV <sub>1</sub> /FVC to <0.7 in eight cases and <LLN in seven cases
<b>MINASIAN, 2013 [17]</b>	Patients with stable chronic heart failure (n=187); sample aged ≥18 years (mean±sd 69±10 years); 83% former or current smokers; 82% reported dyspnoea	Overdiagnosis	Discordant results for COPD diagnosis based on post-bronchodilator FEV <sub>1</sub> /FVC <0.7 but ≥LLN COPD diagnosis despite no evidence of airflow obstruction on spirometry, defined as post-bronchodilator FEV <sub>1</sub> /FVC <0.7 or <LLN Clinical symptoms and risk factor profile of heart failure overlapping with those of true COPD	COPD prevalence varied according to the definition, with 19.8% according to the LLN definition compared to 32.1% using GOLD definition after 3 months of follow-up 32% of patients with history of obstructive lung disease did not have GOLD COPD, and 50% did not meet LLN COPD according to spirometry 74% of patients with misclassified COPD (discordant spirometry) had respiratory symptoms and a smoking history and 64% of non-COPD (with heart failure) also had respiratory symptoms and smoking history Of all patients with known COPD, 42.2% had post-bronchodilator showing asthma only, normal spirometry or other spirometric diagnoses such as restriction
<b>ZWAR, 2011 [19]</b>	Patients (n=445) aged 40–80 years (mean age 65 years), who from GP practice records were considered to have a diagnosis of COPD, emphysema or chronic bronchitis; 30.5% current smokers	Misdiagnosis	COPD diagnosis despite normal spirometry (pre- and post-bronchodilator FEV <sub>1</sub> /FVC >0.7, FVC and FEV <sub>1</sub> >80% of predicted values) or restriction (pre- and post- FEV <sub>1</sub> /FVC >0.7, FVC and FEV <sub>1</sub> <80% of predicted values) or asthma	19.4% of patients with definite COPD according to physicians did not demonstrate COPD on spirometry (2% had asthma, 4% had restriction and 13% had no airflow obstruction)
<b>STARREN, 2012 [21]</b>	Patients referred for spirometry by GPs with definite COPD (n=1156); mean±sd age 61.3±15.6 years; 65% smokers	Misdiagnosis	COPD diagnosis despite normal spirometry (pre- and post-bronchodilator FEV <sub>1</sub> /FVC >0.7, FVC and FEV <sub>1</sub> >80% of predicted values) or restriction (pre- and post- FEV <sub>1</sub> /FVC >0.7, FVC and FEV <sub>1</sub> <80% of predicted values) or asthma	

Continued



Table 2 Continued

First author, year [ref.]	Population details	Terms used	Reason for classification as overdiagnosis	Estimated prevalence of overdiagnosis/misdiagnosis
<b>SPYRATOS, 2016 [11]</b>	Population study (n=3200) including current and former smokers aged >40 years (mean±sd age 60.5±13.4 years); 8.6% had previously physician-diagnosed COPD	Overdiagnosis	COPD diagnosis despite normal spirometry (pre- and post-bronchodilator FEV <sub>1</sub> /FVC >0.7, FVC and FEV <sub>1</sub> >80% of predicted values) or restriction (pre- and post- FEV <sub>1</sub> /FVC >0.7, FVC and FEV <sub>1</sub> <80% of predicted values)	9.6% of group diagnosed with COPD had been overdiagnosed
<b>HILL, 2010 [12]</b>	Patients aged ≥40 years with a smoking history of ≥20 pack-years recruited from primary care practices (n=382); 11% had self-reported pre-existing COPD	Overdiagnosis	COPD diagnosis despite no evidence of airflow obstruction on spirometry, defined as post-bronchodilator FEV <sub>1</sub> /FVC <0.7 and FEV <sub>1</sub> <80% predicted	29.6% with diagnosis of COPD had been overdiagnosed (11.8% of total study population who had medical records reviewed)
<b>GERSHON, 2018 [13]</b>	Random population-based sample of adults aged >40 years (n=1403), including symptomatic subjects with smoking history; 8.8% with physician diagnosis of COPD	Overdiagnosis	COPD diagnosis despite no evidence of airflow obstruction on spirometry, defined as post-bronchodilator FEV <sub>1</sub> /FVC <0.7	Of all participants included in analysis, 5.1% had overdiagnosed COPD
<b>STAFYLA, 2018 [16]</b>	Subjects (n=186) aged >40 years (mean±sd age 62.3±12.6 years) recruited from primary healthcare settings; all current or former smokers; 82.3% had respiratory symptoms, 10.2% with known COPD	Overdiagnosis, misdiagnosis	COPD diagnosis despite no evidence of airflow obstruction on spirometry, defined as post-bronchodilator FEV <sub>1</sub> /FVC <0.7 (no spirometry had been performed before the study)	61.4% of non-COPD subjects according to spirometry had been misdiagnosed with COPD
<b>ROBERTS, 2009 [18]</b>	Patients referred for spirometry with clinical diagnosis of COPD to assess severity or suspected diagnosis for diagnostic confirmation (n=503); mean±sd age 63.8±11.3 years, including symptomatic smokers; 64.8% had received prior diagnosis of COPD	Misdiagnosis	COPD diagnosis despite normal spirometry (pre- and post-bronchodilator FEV <sub>1</sub> /FVC >0.7, FVC and FEV <sub>1</sub> >80% of predicted values) or restriction (pre- and post- FEV <sub>1</sub> /FVC >0.7, FVC and FEV <sub>1</sub> <80% of predicted values)	37.7% of patients that had a clinical diagnosis of COPD had spirometry results incompatible with a diagnosis of COPD

Continued

Table 2 Continued

First author, year [ref.]	Population details	Terms used	Reason for classification as overdiagnosis	Estimated prevalence of overdiagnosis/misdiagnosis
<b>LACASSE, 2012 [20]</b>	Patients discharged from acute care hospitals with a principal diagnosis of COPD (n=1 221); mean±sd age 73.1±12.2 years; 81.9% smokers	Misdiagnosis	COPD diagnosis despite normal spirometry (post-bronchodilator FEV <sub>1</sub> /FVC >0.7)	15.2% of patients discharged with COPD as their principal diagnosis were confirmed to not have COPD according to a review of their medical records and spirometry by two pulmonologists
<b>WALTERS, 2011 [22]</b>	Patients in general practice with either a recorded diagnosis of COPD and/or record of current treatment with the specific COPD therapy tiotropium (n=341); mean±sd age 62.3±8.6 years; 39% current smokers; symptomatic	Misdiagnosis	COPD diagnosis despite normal spirometry (pre- and post-bronchodilator FEV <sub>1</sub> /FVC >0.7, FVC and FEV <sub>1</sub> >80% of predicted values) or restriction (pre- and post- FEV <sub>1</sub> /FVC >0.7, FVC and FEV <sub>1</sub> <80% of predicted values)	31% of patients did not meet the criteria for COPD; of these, three patterns were found on spirometry: 56% had normal lung function, 7% had mild airflow limitation (FEV <sub>1</sub> <80% of predicted), and 37% had restrictive lung function
<b>QUEIROZ, 2012 [23]</b>	Patients recruited from selected primary healthcare centres with no acute respiratory symptoms (n=200); sample aged ≥40 years (mean±sd age 65.0±10.4 years); minimum of 20 pack-years' smoking history or biomass fuel exposure; majority were symptomatic	Misdiagnosis, overdiagnosis	COPD diagnosis despite normal spirometry (post-bronchodilator FEV <sub>1</sub> /FVC >0.7)	14.6% of individuals who did not meet the diagnostic criteria for COPD reported a previous diagnosis of COPD
<b>HEFFLER, 2018 [24]</b>	Consecutive patients referred by GPs for spirometry (n=300); mean±sd age 58.5±18.9 years, including current or former smokers; majority had symptoms; 2.5% physician diagnosis of COPD	Misdiagnosis, overdiagnosis	COPD diagnosis despite normal spirometry (post-bronchodilator FEV <sub>1</sub> /FVC >0.7)	86.7% of those with previous doctor-diagnosis of COPD had non-concordant spirometric patterns
<b>BELLIA, 2003 [31]</b>	Asthmatic subjects from pulmonary or geriatric institutions (n=128); mean±sd age 73.1±6.3 years; most symptomatic	Misdiagnosis	Clinical features of asthma overlapping with those of COPD	19.5% of newly diagnosed asthmatics had received a prior wrong diagnosis of COPD and/or emphysema

## Follow-up spirometry appears normal

LLORDÉS *et al.* [10] found that 16% of newly diagnosed cases of COPD had normal spirometry after 4 weeks of inhalation treatment with formoterol and budesonide. These diagnoses were named false positives or overdiagnosed cases.

## Discussion

### Findings of the review

In this review of 28 studies, the terms “overdiagnosis” and “misdiagnosis” of COPD were used interchangeably to describe the same concepts. These concepts included: 1) physician COPD diagnosis despite normal spirometry (no airflow obstruction at any point) in a situation where i) a normal spirometry result was documented before the study, ii) spirometry had not been performed before the study and the study showed normal spirometry results, or iii) it was unclear whether a spirometry had been performed before the study; 2) discordant results for COPD diagnosis based on different spirometry-based definitions for airflow obstruction (*e.g.* post-bronchodilator  $FEV_1/FVC < 0.7$  or  $FEV_1/FVC < LLN$ ); 3) COPD diagnosis based on pre-bronchodilator spirometry results; 4) comorbidities that have clinical features overlapping with COPD and affect spirometry interpretation; 5) normalisation of abnormal (post-bronchodilator) spirometry at follow-up.

### Comparison with other definitions of overdiagnosis and misdiagnosis

In some COPD studies, “overdiagnosis” has served as an umbrella term to include misdiagnosis. This is in contrast with the “narrow” definition of overdiagnosis, when an asymptomatic person is diagnosed with a (true positive) condition, but the diagnosis does not yield any change in mortality or morbidity for the individual [7]. However, this narrow definition poses a challenge when applied to COPD, as the diagnosis requires the presence of respiratory symptoms and screening of asymptomatic individuals is not recommended.

BRODERSEN *et al.* [32] proposed a definition of overdiagnosis that includes both overdetected and overdefined, both leading to a diagnosis that causes more harm than benefit. “Overdetected” refers to an abnormal finding (*e.g.* a pulmonary nodule) that was never going to cause any harm, abnormalities that do not progress or progress so slowly that they will not cause any morbidity or mortality (*e.g.* non-aggressive prostate cancer), or that resolve spontaneously [33]. By extension, overdetected of COPD describes a diagnosis of COPD that, while correct, is not associated with any harm to the patient (*e.g.* mild emphysematous

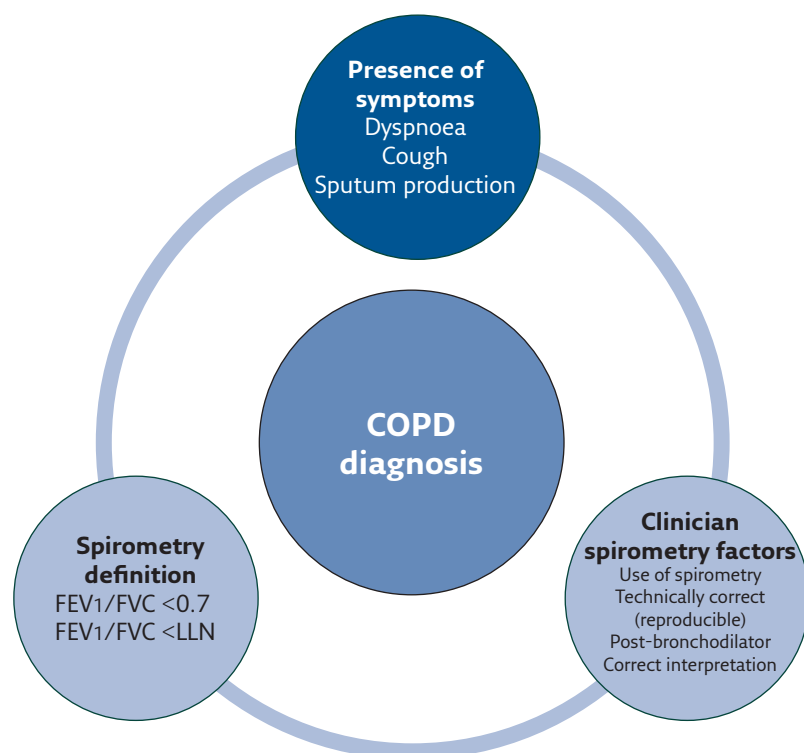
changes on computed tomography of the chest not requiring treatment and not significantly progressing). “Overdefined” refers to lowering the threshold for a risk factor without clear evidence that this results in a net benefit (*e.g.* lowering the threshold for what constitutes a normal blood pressure) or by expanding disease definitions (*e.g.* pre-diabetes) [32].

The current GOLD definition for COPD (updated in 2017) requires the presence of persistent respiratory symptoms (in addition to meeting the spirometric definition of chronic airflow limitation) to make a COPD diagnosis [34]. Applying this definition of COPD is likely to reduce the rates of overdiagnosis in the population-based studies in this review that included asymptomatic patients (table 2). Spirometry-based definitions of airflow obstruction can result in overdefinition and thus overdiagnosis of COPD, *e.g.* when a  $FEV_1/FVC$  ratio threshold of 0.7 is applied in elderly people. There is a potential risk of overdetected if asymptomatic people are screened for COPD, as the connection between mild airflow obstruction in asymptomatic people and subsequent development of symptomatic COPD is unclear. While the importance of early detection of COPD is often emphasised, this relates to detecting COPD early in symptomatic people. There is currently no evidence that supports spirometry screening of asymptomatic people for COPD [35]. A recent study demonstrated that treatment with bronchodilators in mild or moderate COPD can ameliorate the decline of lung function, but this study was conducted in symptomatic patients [36].

### Recommended terminology for future research

Future meta-analyses that aim to explore the extent of COPD diagnostic errors should ideally use consistent terminology. For this purpose, it is important that the definitions of overdiagnosis and misdiagnosis used in the context of COPD are clarified. This review identified one main source of what we propose is COPD overdiagnosis: spirometry-based overdefinition of COPD based on the spirometric definition of airflow obstruction, *e.g.* when a  $FEV_1/FVC$  ratio threshold of 0.7 is applied for airflow obstruction in elderly people. The onus lies on guideline contributors and authority bodies to provide more accurate definitions of airflow obstruction on spirometry.

We identified four sources of misdiagnosis of COPD: 1) physician COPD diagnosis despite normal spirometry; 2) COPD diagnosis based on pre-bronchodilator spirometry results (with normal result at follow-up); 3) comorbidities (*e.g.* heart failure, asthma) that affect spirometry and have clinical features which overlap with COPD; and 4) normalisation of abnormal post-bronchodilator spirometry at follow-up (*e.g.* in asthma).



**Figure 2** Components of a COPD diagnosis.

Figure 2 demonstrates the variety of factors that need to be considered when making a diagnosis of COPD.

## Study limitations

A limitation of some of the studies in this review is that the prevalence of COPD (and

COPD overdiagnosis) was only defined based on a spirometry definition of airflow obstruction (comparable to defining the prevalence of arterial hypertension based on blood pressure measurements in a population), not taking into account that in clinical practice the diagnosis of COPD is a complex issue and the clinical history (symptoms consistent with COPD, exposure to inhaled noxious agent) and ruling out potential differential diagnoses are also essential in making a diagnosis.

While potential adverse events of overtreatment (which can be the result of overdiagnosis) for COPD may not be as severe as for overtreatment of cancer, it is important to keep in mind that all medications have the potential to cause harm and are associated with work that patients need to do to enact treatment recommendations [37].

While this review has focused on overdiagnosis and misdiagnosis, underdiagnosis of COPD is even more common and both overdiagnosis and underdiagnosis can often be explained by underuse or inappropriate use of spirometry [8].

In summary, overdiagnosis of COPD has been used in the reviewed literature to describe both a false positive diagnosis of COPD and overdefinition based on diagnostic criteria. With the introduction of the new GOLD definition of COPD requiring the presence of symptoms, overdefinition and thus overdiagnosis of COPD in population-based studies will probably be reduced. Misdiagnosis of COPD (in addition to underdiagnosis) remains a major diagnostic challenge. To reduce misdiagnosis, clinicians should perform (technically correct) spirometry in all symptomatic patients with clinically suspected COPD.

## Affiliations

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## Author contributions

E.T. Thomas was involved with devising the review methods, conducting electronic searches, screening of abstracts, data extraction and interpretation, and co-drafting of the review. P. Glasziou was involved with devising the review methods, data interpretation and co-drafting the review. C.C. Dobler conceived the original idea, and was involved with devising the review methods, data interpretation and co-drafting the review.

## Conflict of interest

E.T. Thomas has nothing to disclose. P. Glasziou reports a 5-year Program Grant (2017–2021) on overdiagnosis from the Australian National Health and Medical Research Council, outside the submitted work. C.C. Dobler has nothing to disclose.

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